Complete Summary

GUIDELINE TITLE

Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease.

BIBLIOGRAPHIC SOURCE(S)

Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization, National Heart, Lung and Blood Institute; 2005. 115 p. [62 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization, National Heart, Lung and Blood Institute; 2004. 100 p.

Each year, a new updated report will be posted; a revision of the entire document will be prepared approximately every 5 years. According to the developer, a revision of the entire document has been initiated and is scheduled to be completed in 2006.

Information regarding GOLD, Phase IV is available at the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Web site.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- On November 18, 2005, the U.S. Food and Drug Administration (FDA) notified manufacturers of Advair Diskus, Foradil Aerolizer, and Serevent Diskus to update their existing product labels with new warnings and a Medication

Guide for patients to alert health care professionals and patients that these medicines may increase the chance of severe asthma episodes, and death when those episodes occur. All of these products contain long-acting beta2-adrenergic agonists (LABA). Even though LABAs decrease the frequency of asthma episodes, these medicines may make asthma episodes more severe when they occur. A Medication Guide with information about these risks will be given to patients when a prescription for a LABA is filled or refilled. See the FDA Web site for more information.

- On February 17, 2006, BMS notified the U.S. Food and Drug Administration (FDA) and healthcare professionals about proposed changes to the prescribing information for Tequin (gatifloxacin), including an updating of the existing WARNING on hypoglycemia (low blood sugar) and hyperglycemia (high blood sugar), and a CONTRAINDICATION for use in diabetic patients. The changes also include information identifying other risk factors for developing low blood sugar and high blood sugar, including advanced age, renal insufficiency, and concomitant glucose-altering medications while taking Tequin. See the FDA Web site for more information.
- On June 30, 2006, the Food and Drug Administration notified healthcare professionals and patients that it completed its safety assessment of Ketek (telithromycin), indicated for the treatment of acute exacerbation of chronic bronchitis, acute bacterial sinusitis, and community acquired pneumonia of mild to moderate severity, including pneumonia caused by resistant strep infections. The drug has been associated with rare cases of serious liver injury and liver failure with four reported deaths and one liver transplant after the administration of the drug. FDA determined that additional warnings are required and the manufacturer is revising the drug labeling to address this safety concern. FDA is advising both patients taking Ketek and their doctors to be on the alert for signs and symptoms of liver problems. Patients experiencing such signs or symptoms should discontinue Ketek and seek medical evaluation, which may include tests for liver function. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Chronic obstructive pulmonary disease (COPD)

Note: The focus of this report is primarily on COPD caused by inhaled particles and gases, the most common of which worldwide is tobacco smoke. Poorly reversible airflow limitation associated with bronchiectasis, cystic fibrosis, tuberculosis, or asthma is not included except insofar as these conditions overlap with COPD.

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Emergency Medicine
Family Practice
Internal Medicine
Preventive Medicine
Pulmonary Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Nurses
Physician Assistants
Physicians
Public Health Departments
Respiratory Care Practitioners

GUIDELINE OBJECTIVE(S)

- To recommend effective chronic obstructive pulmonary disease (COPD) management and prevention strategies for use in all countries
- To increase awareness of the medical community, public health officials, and the general public that COPD is a public health problem
- To decrease morbidity and mortality from COPD through implementation and evaluation of effective programs for diagnosis and management
- To improve prevention and management of COPD through a concerted worldwide effort of people involved in all facets of health care and health care policy
- To encourage a renewed research interest in this highly prevalent disease

TARGET POPULATION

Individuals with chronic obstructive pulmonary disease

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Diagnosis

1. Initial diagnosis:
    - Assessment of symptoms
    - Medical history
    - Physical examination
    - Measurement of airflow limitation
    - Assessment of severity
    - Additional investigations
    - Differential diagnosis
2. Ongoing monitoring and assessment:
    - Monitor disease progression and development of complications
    - Monitor pharmacotherapy and other medical treatment
    - Monitor exacerbation history
    - Monitor comorbidities

Risk Factor Reduction

1. Smoking prevention and cessation
2. Occupational exposures
3. Indoor/outdoor air pollution

Treatment/Management of Stable Chronic Obstructive Pulmonary Disease (COPD)

1. Education:
    - Goals and educational strategies
    - Components of an education program
2. Pharmacologic treatment
    - Bronchodilators
    - Glucocorticosteroids
    - Other pharmacologic treatments
3. Non-pharmacologic treatment:
    - Rehabilitation
    - Oxygen therapy
    - Ventilatory support
    - Surgical treatments

Management of Exacerbations

1. Diagnosis and assessment of severity:
    - Medical history
    - Assessment of severity
2. Home management:
    - Bronchodilator therapy
    - Glucocorticosteroids
3. Hospital management:
    - Emergency department or hospital
4. Hospital discharge and follow-up
5. Antibiotics

MAJOR OUTCOMES CONSIDERED

- Mortality

- Morbidity, including physicians visits, emergency department visits, and hospitalizations
- Economic cost and social burden

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

In September 1997, several members of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Expert Panel met with a consultant to develop a comprehensive set of search terms to build a database of chronic obstructive pulmonary disease (COPD) literature. A database and a computer program to search the world literature on COPD were developed.

2003 Update

The 2003 update included review of publications from June 2000 (approximate time of completion of the 2001 report) through March 2003.

2004 Update

The 2004 update includes review of publications from April through December 2003 (January to March 2003 were included in the 2003 update).

2005 Update

The 2005 update includes review of publications from January to December 2004. The process (identical to that used for previous updates) included a Pub Med search using search fields established by the Committee: 1) COPD OR chronic bronchitis OR emphysema, All Fields, All Adult, 19+ years, only items with abstracts, Clinical Trial, Human, sorted by Authors; and 2) COPD OR chronic bronchitis OR emphysema AND systematic, All fields, All adult, 19+ years, only items with abstracts, Human, sorted by Author. In addition, publications in peer review journals not captured by Pub Med could be submitted to individual members of the Committee providing an abstract and the full paper were submitted in (or translated into) English.

NUMBER OF SOURCE DOCUMENTS

2003 Update

241 articles met the search criteria. Of these, 36 papers were identified to have an impact on the GOLD report.

2004 Update

140 articles met the search criteria. Of these, 16 papers were identified to have an impact on the GOLD report.

2005 Update

131 articles met the search criteria. Of these, 10 papers were identified to have an impact on the GOLD report.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Description of Levels of Evidence

A. Randomized controlled trials (RCTs). Rich body of data.
   Definition: Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B. Randomized controlled trials. Limited data.
   Definition: Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C. Nonrandomized trials. Observational studies.
   Definition: Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D. Panel consensus. Judgment.
   Definition: This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Nominal Group Technique)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The first step toward developing the consensus Workshop Report was to review the multiple chronic obstructive pulmonary disease (COPD) guidelines already published. The National Heart, Lung, and Blood Institute (NHLBI) collected these guidelines and prepared a summary table of similarities and differences between the documents. Where agreement existed, the Expert Panel drew on these existing documents for use in the Workshop Report. Where major differences existed, the Expert Panel agreed to carefully examine the scientific evidence to reach an independent conclusion. The Workshop Report is based on the best-validated current concepts of COPD pathogenesis and the available evidence on the most appropriate management and prevention strategies. It has been developed by individuals with expertise in COPD research and patient care and extensively reviewed by many experts and scientific societies.

2005 Update

All members of the Committee received a summary of citations and all abstracts. Each abstract was assigned to 2 Committee members (members were not assigned to a paper where he/she appears as an author), although any member was offered the opportunity to provide an opinion on any abstract. Members evaluated the abstract or, up to her/his judgment, the full publication, by answering specific written questions from a short questionnaire, and to indicate if the scientific data presented impacted on recommendations in the GOLD Workshop Report. If so, the member was asked to specifically identify modifications that should be made. The GOLD Science Committee met on a regular basis to discuss each individual publication that was indicated by at least 1 member of the Committee to have an impact on COPD, and to reach a consensus on the changes in the report. Disagreements were decided by vote.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The cost effectiveness of education programs for chronic obstructive pulmonary disease (COPD) is highly dependent on local factors that influence the cost of access to medical services and that will vary substantially between countries. In one cost-benefit analysis of education provided to hospital patients with COPD, an information package resulted in increased knowledge of COPD and reduced use of health services, including reductions of hospital readmissions and general practice consultations. The education package involved training patients to increase knowledge of COPD, medication usage, precautions for exacerbations, and peak flow monitoring technique. However, this study was undertaken in a heterogeneous group of patients - 65% were smokers and 88% were judged to have an asthmatic component to their disease - and these findings may not hold true for a "pure" COPD population. In a study of mild to moderate COPD patients at an out-patient clinic, patient education involving one four-hour group session

followed by one to two individual nurse and physiotherapist sessions improved patient outcomes and reduced costs in a 12-month follow-up.

The guideline developer reviewed the economic and social burden of COPD: Because COPD is highly prevalent and can be severely disabling, direct medical expenditures and the indirect costs of morbidity and premature mortality from COPD can represent a substantial economic and social burden for societies and public and private insurance payers worldwide. Nevertheless, very little quantitative information concerning the economic and social burden of COPD is available in the literature (at the time the guideline was developed). Refer to the original guideline document for information from cost of illness studies (data is available from the United States and some European countries) and data regarding COPD in the context as a leading cause of Disability-Adjusted Life Years (DALYs) lost worldwide.

METHOD OF GUIDELINE VALIDATION

Comparison with Guidelines from Other Groups
External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The final draft document was submitted for review to individuals and medical societies interested in the management of COPD. The reviewers' comments were incorporated, as appropriate, into the final document by the Chair in cooperation with members of the Expert Panel. Prior to its release for publication, the Report was reviewed by the National Heart, Lung, and Blood Institute and the World Health Organization (WHO).

2005 Update

Prior to its release, the proposed modifications to the GOLD Workshop Report (updated 2005) were submitted to the GOLD Executive Committee for approval.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC): The recommendations presented below were taken from the GOLD Executive Summary. Changes made to the original guideline in 2003, 2004, and 2005 are also presented.

The levels of evidence (A-D) are defined at the end of "Major Recommendations" field.

Summary of New Recommendations in the 2005 Update

Of the 10 papers identified as having an impact on the report, 5 confirmed an existing statement and were added as references. Five papers introduced

information that required a new statement to be added to the report (page numbers refer to the full original guideline document):

- Page 67--Add sentence: In a study of mild to moderate chronic obstructive pulmonary disease (COPD) patients at an out-patient clinic, patient education involving one four-hour group session followed by one to two individual nurse- and physiotherapist-sessions improved patient outcomes and reduced costs in a 12-month follow-up.
- Page 70--Add sentence: Twenty-one days of inhaled tiotropium, 18 mg/day as a dry powder does not reduce mucus clearance from the lungs.
- Page 71--Add sentence: Short-term treatment with a combined inhaled glucocorticosteroid and long-acting beta2-agoinst resulted in greater control of lung function and symptoms than combined anticholinergic and short-acting beta2-agoist.
- Page 73--Change paragraph on immunoregulators to read: Studies using an immunostimulator in COPD show a decrease in the severity and frequency of exacerbations. However, additional studies to examine the long term effects of this therapy are required before regular use can be recommended (Evidence B).
- Page 93--Add sentence: Early outpatient pulmonary rehabilitation after hospitalization for COPD exacerbation results in exercise capacity and health status improvements at three months.

A major new segment appears in Chapter 5-4 on antibiotics in treatment of COPD exacerbations (page 94). The material was prepared by the GOLD Science Committee which gratefully acknowledges the opportunity to review a statement on this topic prepared by the European Respiratory Society and provided to the Committee.

An Appendix includes a report on outcome measures for COPD to encourage comments and input from the scientific community to prepare for the full revision of the report, scheduled to appear in mid-2006. The many individuals who participated in preparation of this report are listed in the document.

Summary of New Recommendations in the 2004 Update

The most important changes can be summarized as follows:

- After a retrospective review of the literature triggered by a 2003 publication, a statement regarding the use of walking aids in patients with COPD has been added (Evidence C).
- The role of oxygen supplementation before, during, or after exercise has been discussed with the suggestion that there is no evidence of benefit from using short burst oxygen for symptomatic relief before or after exercise (Evidence B).
- The recommendation for lung volume reduction surgery (LVRS) has been modified, reporting that it does not improve life expectancy but improves exercise capacity in patients with predominant upper lobe emphysema and a low post rehabilitation exercise capacity, and may improve global health status in patients with heterogeneous emphysema.

- Based on a retrospective review of the literature triggered by new articles appearing after 2001, a new section has been added on recommendations for surgery in COPD.
- Finally, the GOLD science committee acknowledges the publication of the American Thoracic Society/European Respiratory Society (ATS/ERS) position paper on COPD, which overall confirms almost all recommendations of the GOLD Workshop, but also expands some topics not covered or only marginally touched by the GOLD Workshop Report.

Summary of Recommendations in the 2003 Update

The major modifications introduced to the management section included:

- The position of long-acting and short acting bronchodilators, including the introduction of the new long-acting anticholinergic, tiotropium
- The position of inhaled glucocorticosteroids and combination of inhaled long-acting beta2-agonists/glucocorticosteroids
- Evidence related to length of pulmonary rehabilitation programs
- Home vs. hospital care for COPD exacerbations

Because of difficulties encountered using the 2001 GOLD classification by severity in the dissemination process, and in line with the recommendations that are being proposed by the COPD Guidelines Committee nominated jointly by the European Respiratory Society and by the American Thoracic Society, the classification was maintained, but the stages of severity were renamed into 0=At Risk, I=Mild, II=Moderate, III=Severe, and IV=Very severe to replace stages At Risk (0), Mild (I), Moderate (IIA, IIB), and Severe (III) respectively.

The 2001 GOLD Workshop Report included the recommendation to use regular treatment with bronchodilators for moderate to severe COPD, mentioning that long-acting bronchodilators were more convenient than short-acting bronchodilators. Based on publications that appeared since June 2000, the updated 2003 GOLD Workshop Report recommends for moderate to very severe COPD use of regular treatment with long-acting bronchodilators, including tiotropium, rather than short-acting bronchodilators (Evidence A).

The 2001 Report included the recommendation to use inhaled glucocorticosteroids for patients with moderate COPD or more, providing they had a spirometric response to a short-term course of steroids and/or an FEV_1 (forced expiratory volume in one second)<50% predicted and frequent exacerbations. This recommendation was assigned (Evidence B) reflecting the inconsistency of response to inhaled glucocorticosteroids reported in the literature. Based on publications appearing since June 2000, the 2003 Report recommends use of inhaled glucocorticosteroids only in patients with severe and very severe (Stages III and IV) COPD (called IIB and III in the 2001 Report) and frequent exacerbations, assigning to the recommendation (Evidence A), reflecting the consistency of the response to inhaled glucocorticosteroids in more severe patients reported in the literature.

The 2001 Report did not include a specific recommendation for the duration of rehabilitation programs. Based on publications appearing since June 2000, the 2003 Report recommends a duration of at least 2 months for rehabilitation

programs, assigning to the recommendation (Evidence B), reflecting the limited number of studies available.

The 2001 GOLD Workshop Report did not include a specific recommendation for the nurse administered home care as an alternative to hospitalization of patients with COPD exacerbations. Based on publications appearing since June 2000, the 2003 GOLD Workshop Report suggests that nurse-administered home care represents an effective and practical alternative to hospitalization in selected patients with exacerbations of COPD without acidotic respiratory failure. However, because the exact criteria for home compared to hospital treatment remains uncertain, and may vary by health care setting, no level of evidence was assigned to this recommendation.

Finally, the Committee identified important issues for which the new scientific evidence reviewed was considered insufficient to change the 2001 Report, but that were judged as priority issues to be addressed in the 2004 update. These include antibiotic treatment of COPD exacerbations, step-up/down of pharmacological treatment, use of walking aids for rehabilitation, and anesthesia in severe COPD patients undergoing surgery.

Overall Guideline Recommendations (2005 Update)

I. Classification

Classification of COPD by Severity

Stage 0 [At Risk]:

- Normal spirometry
- Chronic symptoms (cough, sputum, production)

Stage I [Mild COPD]:

- $FEV_1/FVC < 70\%$
- $FEV_1 \geq 80\%$ predicted
- With or without chronic symptoms (cough, sputum production)

Stage II [Moderate COPD]:

- $FEV_1/FVC < 70\%$
- $50\% \leq FEV_1 < 80\%$ predicted
- With or without chronic symptoms (cough, sputum production)

Stage III [Severe COPD]:

- $FEV_1/FVC < 70\%$
- $30\% \leq FEV_1 < 50\%$ predicted
- With or without chronic symptoms (cough, sputum production)

Stage IV [Very Severe COPD]:

- $FEV_1/FVC < 70\%$
- $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure

(Abbreviations: FVC = forced vital capacity, FEV_1 = forced expiratory volume in one second)

II. Assess and Monitor Disease

Key Points

- Diagnosis of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with or without the presence of symptoms.
- Patients who have chronic cough and sputum production with a history of exposure to risk factors should be tested for airflow limitation, even if they do not have dyspnea.
- For the diagnosis and assessment of COPD, spirometry is the gold standard as it is the most reproducible, standardized, and objective way of measuring airflow limitation. $FEV_1/FVC < 70\%$ and a postbronchodilator $FEV_1 < 80\%$ predicted confirms the presence of airflow limitation that is not fully reversible.
- Health care workers involved in the diagnosis and management of COPD patients should have access to spirometry.
- Measurement of arterial blood gas tensions should be considered in all patients with $FEV_1 < 40\%$ predicted or clinical signs suggestive of respiratory failure or right heart failure.

Diagnosis

A diagnosis of COPD should be considered in any patient who has cough, sputum production, or dyspnea, and/or a history of exposure to risk factors for the disease. The diagnosis is confirmed by an objective measure of airflow limitation, preferably spirometry.

Key Indicators for Considering a Diagnosis of COPD

- Chronic cough: Present intermittently or every day. Often present throughout the day; seldom only nocturnal.
- Chronic sputum production: Any pattern of chronic sputum production may indicate COPD.
- Dyspnea that is:
  - Progressive (worsens over time)
  - Persistent (present every day)
  - Described by the patient as: "increased effort to breathe," "heaviness," "air hunger," or "gasping"
  - Worse on exercise
  - Worse during respiratory infections
- History of exposure to risk factors, especially:
  - Tobacco smoke
  - Occupational dusts and chemicals
  - Smoke from home cooking and heating fuels

Medical History

A detailed medical history of a new patient known or thought to have COPD should assess:

- Exposure to risk factors
- Past medical history, including asthma, allergy, sinusitis or nasal polyps, respiratory infections in childhood, and other respiratory diseases
- Family history of COPD or other chronic respiratory disease
- Pattern of symptom development
- History of exacerbations or previous hospitalizations for respiratory disorder
- Presence of comorbidities, such as heart disease and rheumatic disease, that may also contribute to restriction of activity
- Appropriateness of current medical treatments
- Impact of disease on patient's life, including limitation of activity; missed work and economic impact; effect on family routines; and feelings of depression or anxiety
- Social and family support available to the patient
- Possibilities for reducing risk factors, especially smoking cessation

Physical Examination: Though an important part of patient care, a physical examination is rarely diagnostic in COPD. Physical signs of airflow limitation are rarely present until significant impairment of lung function has occurred, and their detection has a relatively low sensitivity and specificity.

Measurement of Airflow Limitation: To help identify patients earlier in the course of the disease, spirometry should be performed for patients who have chronic cough and sputum production and a history of exposure to risk factors, even if they do not have dyspnea. Spirometry should measure the maximal volume of air forcibly exhaled from the point of maximal inhalation (forced vital capacity [FVC]) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV_1), and the ratio of these two measurements (FEV_1/FVC) should be calculated. Patients with COPD typically show a decrease in both FEV_1 and FVC. The presence of a postbronchodilator FEV_1 <80% of the predicted value in combination with an FEV_1/FVC <70% confirms the presence of airflow limitation that is not fully reversible. The FEV_1/FVC on its own is a more sensitive measure of airflow limitation, and an FEV_1/FVC <70% is considered an early sign of airflow limitation in patients whose FEV_1 remains normal ($\geq$80% predicted). This approach to defining airflow limitation is a pragmatic one in view of the fact that universally applicable reference values for FEV_1 and FVC are not available.

Assessment of Severity: Assessment of severity (see Table 2 in the Executive Summary) is based on the patient's level of symptoms, severity of the spirometric abnormality, and the presence of complications such as respiratory failure and right heart failure.

Additional Investigations: For patients in Stage II: Moderate COPD and beyond, the following additional investigations may be useful.

Bronchodilator reversibility testing: Generally performed only once, at the time of diagnosis, this test is useful to help rule out a diagnosis of asthma, to establish a patient's best attainable lung function, to gauge a patient's prognosis, and to guide treatment decisions. However, even patients who do not show a significant FEV_1 response to a short-acting bronchodilator test may benefit symptomatically from long-term bronchodilator treatment.

Chest x-ray: A chest x-ray is seldom diagnostic in COPD unless obvious bullous disease is present, but it is valuable in excluding alternative diagnoses. Computed tomography (CT) of the chest is not routinely recommended. However, when there is doubt about the diagnosis of COPD, high resolution computed tomography (HRCT) might help in the differential diagnosis. In addition, if a surgical procedure such as bullectomy or lung volume reduction is contemplated, chest computed tomography is most helpful.

Arterial blood gas measurement: In advanced COPD, measurement of arterial blood gases is important. This test should be performed in patients with FEV_1 <40% predicted or with clinical signs suggestive of respiratory failure or right heart failure. Clinical signs of respiratory failure or right heart failure include central cyanosis, ankle swelling, and an increase in the jugular venous pressure. Clinical signs of hypercapnia are extremely nonspecific outside of exacerbations. Respiratory failure is indicated by a PaO_2 <8.0 kilopascals (kPa) (60 millimeters of mercury [mm Hg]) with or without $PaCO_2$ >6.7 kPa (50 mm Hg) while breathing air at sea level. Measurement of arterial blood gases should be obtained by arterial puncture; finger or ear oximeters for assessing arterial oxygen saturation (SaO_2) are less reliable.

Alpha-1 antitrypsin deficiency screening: In patients who develop COPD at a young age (younger than 45 years) or who have a strong family history of the disease, it may be valuable to identify coexisting alpha-1 antitrypsin deficiency. This could lead to family screening and appropriate counseling.

Differential Diagnosis: A major differential diagnosis is asthma. In some patients with chronic asthma, a clear distinction from COPD is not possible using current imaging and physiological testing techniques. In these cases, current management is similar to that of asthma. Other potential diagnoses are usually easier to distinguish from COPD.

Suggestive features for respective diseases are presented below:

COPD

- Onset in mid-life
- Symptoms slowly progressive
- Long smoking history
- Dyspnea during exercise
- Largely irreversible airflow limitation

Asthma

- Onset early in life (often childhood)
- Symptoms vary from day to day
- Symptoms at night/early morning
- Allergy, rhinitis, and/or eczema also present
- Family history of asthma
- Largely reversible airflow limitation

Congestive Heart Failure

- Fine basilar crackles on auscultation
- Chest x-ray shows dilated heart, pulmonary edema
- Pulmonary function tests indicate volume restriction, not airflow limitation

Bronchiectasis

- Large volumes of purulent sputum
- Commonly associated with bacterial infection
- Coarse crackles/clubbing on auscultation
- Chest x-ray/computed tomography shows bronchial dilation, bronchial wall thickening

Tuberculosis

- Onset all ages
- Chest x-ray shows lung infiltrate or nodular lesions
- Microbiological confirmation
- High local prevalence of tuberculosis

Obliterative Bronchiolitis

- Onset in younger age, nonsmokers
- May have history of rheumatoid arthritis or fume exposure
- Computed tomography on expiration shows hypodense areas

Diffuse Panbronchiolitis

- Most patients are male and nonsmokers
- Almost all have chronic sinusitis
- Chest x-ray and high resolution computed tomography (HRCT) show diffuse small centrilobular nodular opacities and hyperinflation

Note: These features tend to be characteristic of the respective diseases, but do not occur in every case. For example, a person who has never smoked may develop COPD (especially in the developing world, where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even elderly patients.

Ongoing Monitoring and Assessment

Monitor Disease Progression and Development of Complications: COPD is usually a progressive disease, and a patient's lung function can be expected to worsen over time, even with the best available care. Symptoms

and objective measures of airflow limitation should be monitored for development of complications and to determine when to adjust therapy.

Follow-up visits should include a discussion of new or worsening symptoms. Spirometry should be performed if there is a substantial increase in symptoms or a complication. Measurement of arterial blood gas tensions should be considered in all patients with an FEV_1 <40% predicted or clinical signs of respiratory failure or right heart failure. Elevation of the jugular venous pressure and the presence of pitting ankle edema are often the most useful findings suggestive of right heart failure in clinical practice. Measurement of pulmonary arterial pressure is not recommended in clinical practice as it does not add practical information beyond that obtained from a knowledge of PaO_2.

Monitor Pharmacotherapy and Other Medical Treatment: In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen. Dosages of various medications, adherence to the regimen, inhaler technique, effectiveness of the current regime at controlling symptoms, and side effects of treatment should be monitored.

Monitor Exacerbation History: Frequency, severity, and likely causes of exacerbations should be evaluated. Increased sputum volume, acutely worsening dyspnea, and the presence of purulent sputum should be noted. Severity can be estimated by the increased need for bronchodilator medication or glucocorticosteroids and by the need for antibiotic treatment. Hospitalizations should be documented, including the facility, duration of stay, and any use of critical care or intubation.

Monitor Comorbidities: In treating patients with COPD, it is important to consider the presence of concomitant conditions such as bronchial carcinoma, tuberculosis, sleep apnea, and left heart failure. The appropriate diagnostic tools (chest radiograph, electrocardiogram, etc.) should be used whenever symptoms (e.g., hemoptysis) suggest one of these conditions.

III. Reduce Risk Factors

Key Points

- Reduction of total personal exposure to tobacco smoke, occupational dusts, and chemicals, and indoor and outdoor air pollutants are important goals to prevent the onset and progression of COPD.
- Smoking cessation is the single most effective -- and cost-effective -- intervention to reduce the risk of developing COPD and stop its progression (Evidence A).
- Brief tobacco dependence treatment is effective (Evidence A) and every tobacco user should be offered at least this treatment at every visit to the health care provider.
- Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment (Evidence A).

- Several effective pharmacotherapies for tobacco dependence are available (Evidence A), and at least one of these medications should be added to counseling if necessary and in the absence of contraindications.
- Progression of many occupationally induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases (Evidence B).

Smoking Prevention and Cessation

Comprehensive tobacco control policies and programs with clear, consistent, and repeated nonsmoking messages should be delivered through every feasible channel. Legislation to establish smoke-free schools, public facilities, and work environments should be encouraged by government officials, public health workers, and the public.

Smoking cessation is the single most effective -- and cost-effective -- way to reduce the risk of developing COPD and stop its progression. Even a brief, three-minute period of counseling to urge a smoker to quit can be effective, and at the very least this should be done for every smoker at every visit. Health education, public policy, and information dissemination programs are all vital components in a comprehensive cessation effort.

Guidelines for Smoking Cessation: Guidelines for smoking cessation were published by the United States Agency for Health Care Policy and Research (AHCPR) (now the Agency for Healthcare Research and Quality [AHRQ]) in 1996 and updated in 2000 by the United States Public Health Service in "Treating Tobacco Use and Dependence: A Clinical Practice Guideline."

Smoking Cessation Intervention Process: The Public Health Service Report recommends a five-step program for intervention (see "Strategies to Help the Patient Willing to Quit Smoking", below), which provides a strategic framework helpful to health care providers interested in helping their patients stop smoking. Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment (Evidence A).

Pharmacotherapy: Numerous effective pharmacotherapies for smoking cessation now exist (Evidence A). Except in the presence of special circumstances, pharmacotherapy is recommended when counseling is not sufficient to help patients quit smoking. Numerous studies indicate that nicotine replacement therapy in any form (nicotine gum, inhaler, nasal spray, transdermal patch, sublingual tablet, or lozenge) reliably increases long-term smoking abstinence rates. The antidepressants bupropion and nortriptyline have also been shown to increase long-term quit rates, although fewer studies have been conducted with these medications. The effectiveness of the antihypertensive drug clonidine is limited by side effects. Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers fewer than 10 cigarettes/day, and pregnant and adolescent smokers.

Strategies to Help the Patient Willing to Quit Smoking

1. ASK: Systematically identify all tobacco users at every visit. Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.
2. ADVISE: Strongly urge all tobacco users to quit. In a clear, strong, and personalized manner, urge every tobacco user to quit.
3. ASSESS: Determine willingness to make a quit attempt. Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).
4. ASSIST: Aid the patient in quitting. Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.
5. ARRANGE: Schedule follow-up contact. Schedule follow-up contact, either in person or via telephone.

Occupational Exposures

Although it is not known how many individuals are at risk of developing respiratory disease from occupational exposures in either developing or developed countries, many occupationally-induced respiratory disorders can be reduced or controlled through a variety of strategies aimed at reducing the burden of inhaled particles and gases. Emphasis should be on primary prevention, which is best achieved by the elimination or reduction of exposures to various substances in the workplace. Secondary prevention, achieved through epidemiologic surveillance and early case detection, is also of great importance.

Indoor/Outdoor Air Pollution

Individuals experience diverse indoor and outdoor environments throughout the day, each of which has its own unique set of air contaminants. Although outdoor and indoor air pollution are generally thought of separately, the concept of total personal exposure may be more relevant for COPD. Reducing the risk from indoor and outdoor air pollution requires a combination of public policy and protective steps taken by individual patients.

The health care provider should consider susceptibility (including family history, exposure to indoor/outdoor pollution) for each individual patient. Those who are at high risk should avoid vigorous exercise outdoors during pollution episodes. If various solid fuels are used for cooking and heating, adequate ventilation should be encouraged. Persons with severe COPD should monitor public announcements of air quality and should stay indoors when air quality is poor. Under most circumstances, health care providers should not suggest respiratory protection as a method for reducing the risks of ambient air pollution. Air cleaners have not been shown to have health benefits, whether directed at pollutants generated by indoor sources or at those brought in with outdoor air.

IV. Manage Stable COPD

Key Points

- The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease.
- For patients with COPD, health education can play a role in improving skills, ability to cope with illness, and health status. It is effective in accomplishing certain goals, including smoking cessation (Evidence A).
- None of the existing medications for COPD has been shown to modify the long-term decline in lung function that is the hallmark of this disease (Evidence A). Therefore, pharmacotherapy for COPD is used to decrease symptoms and/or complications.
- Bronchodilator medications are central to the symptomatic management of COPD (Evidence A). They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms.
- The principal bronchodilator treatments are beta2-agonist, anticholinergics, theophylline, and a combination of one or more of these drugs (Evidence A).
- Regular treatment with long-acting bronchodilators is more effective than and convenient than treatment with short-acting bronchodilators, but more expensive (Evidence A).
- The addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with an FEV_1 <50% predicted (Stage III: Severe COPD and Stage IV Very Severe COPD) and repeated exacerbations (Evidence A).
- Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio (Evidence A).
- All COPD patients benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (Evidence A).
- The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival (Evidence A).

The overall approach to managing stable COPD should be characterized by a stepwise increase in treatment, depending on the severity of the disease. The management strategy is based on an individualized assessment of disease severity and response to various therapies. Disease severity is determined by the severity of symptoms and airflow limitation, as well as other factors such as the frequency and severity of exacerbations, complications, respiratory failure, comorbidities (cardiovascular disease, sleep related disorders, etc.), and the general health status of the patient. Treatment also depends on the patient's educational level and willingness to apply the recommended management, on cultural and local conditions, and on the availability of medications.

Education

Although patient education alone does not improve exercise performance or lung function, it can play a role in improving skills, ability to cope with illness, and health status. In addition, patient education is effective in accomplishing certain specific goals, including smoking cessation (Evidence A), initiating

discussions and understanding of advance directives and end-of-life issues (Evidence B), and improving patient responses to exacerbations (Evidence B).

Education may take place in many settings: consultations with physicians or other health care workers, home care or outreach programs, and comprehensive pulmonary rehabilitation programs. It should be tailored to the needs and environment of the patient, interactive, directed at improving quality of life, simple to follow, practical, and appropriate to the intellectual and social skills of the patient and the caregiver. The topics that seem most appropriate for an education program to cover include: smoking cessation; basic information about COPD and pathophysiology of the disease; general approach to therapy and specific aspects of medical treatment; self-management skills; strategies to help minimize dyspnea; advice about when to seek help; self-management and decision-making in exacerbations; and advance directives and end-of-life issues.

Pharmacologic Treatment

<table>
<tr><td colspan="5">Therapy at Each Stage of COPD</td></tr>
<tr><td>Old</td><td>0: At Risk</td><td>I: Mild</td><td colspan="2">II: Modera</td></tr>
<tr><td></td><td></td><td></td><td>IIA</td><td></td></tr>
<tr><td>New</td><td>0: At Risk</td><td>I: Mild</td><td colspan="2">II: Moderate</td></tr>
<tr><td>Characteristics</td><td>• Chronic symptoms
• Exposure to risk factors
• Normal spirometry</td><td>• FEV_1/FVC <70%
• $FEV_1 \geq 80\%$
• With or without symptoms</td><td>• FEV_1/FVC <70%
• 50% $\leq FEV_1 < 80\%$
• With or without symptoms</td><td>•
•
•</td></tr>
<tr><td rowspan="4"></td><td colspan="4">Avoidance of risk factor(s); Influenza vacc</td></tr>
<tr><td rowspan="3"></td><td colspan="3">Add short-acting bronchodila</td></tr>
<tr><td rowspan="2"></td><td colspan="2">Add regular treatment with o
Add rehabilitation</td></tr>
<tr><td></td><td>Add exac</td></tr>
</table>

Pharmacologic therapy (see the table above, also Table 8 in the Executive Summary) is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD (see Table 10 in the Executive Summary) has been shown to modify the long-term decline in lung

function that is the hallmark of this disease (Evidence A). However, this should not preclude efforts to use medications to control symptoms.

Bronchodilators

Bronchodilator medications are central to the symptomatic management of COPD (Evidence A) (see Table 9 in the Executive Summary). They are given either on an as-needed basis for relief of persistent or worsening symptoms, or on a regular basis to prevent or reduce symptoms. Dose-response relationships using the FEV_1 as the outcome are relatively flat in all classes of bronchodilators. Side effects are pharmacologically predictable and dose-dependent. Adverse effects are less likely and resolve more rapidly after treatment withdrawal with inhaled than with oral treatment. When treatment is given by the inhaled route, attention to effective drug delivery and training in inhaler technique is essential.

Bronchodilators drugs commonly used in treating COPD include:

<u>Beta2-agonists</u>:

Short-acting

- Fenoterol
- Salbutamol (albuterol)
- Terbutaline

Long-acting

- Formoterol
- Salmeterol

<u>Anticholinergics</u>

Short-acting

- Ipratropium bromide
- Oxitropium bromide

Long-acting

- Tiotropium

<u>Combination short-acting beta2-agonists plus anticholinergic in one inhaler</u>

- Fenoterol/Ipratropium
- Salbutamol/Ipratropium

<u>Methylxanthines</u>

- Aminophylline (slow release preparations)

- Theophylline (slow release preparations)

Inhaled glucocorticosteroids

- Beclomethasone
- Budesonide
- Fluticasone
- Triamcinolone

Combination long-acting beta2-agonists plus glucocorticosteroids in one inhaler

- Formoterol/Budesonide
- Salmeterol/Fluticasone

Systemic glucocorticosteroids

- Prednisone
- Methyl-prednisone

The choice depends on the availability of the medication and the patient's response. All categories of bronchodilators have been shown to increase exercise capacity in COPD, without necessarily producing significant changes in FEV_1 (Evidence A). Regular treatment with long acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators, but more expensive (Evidence A). Regular use of a long-acting beta2-agonist or long-acting anticholinergic improves health status. Theophylline is effective in COPD, but due to its potential toxicity, inhaled bronchodilators are preferred when available. All studies that have shown efficacy of theophylline in COPD were done with slow-release preparations.

Combining drugs with different mechanisms and durations of action might increase the degree of bronchodilation for equivalent or lesser side effects. A combination of a short-acting beta2-agonist and an anticholinergic produces greater and more sustained improvements in FEV_1 than either alone and does not produce evidence of tachyphylaxis over 90 days of treatment (Evidence A).

Combination of a beta2-agonist, an anticholinergic, and/or theophylline may produce additional improvements in lung function and health status. Increasing the number of drugs usually increases costs, and an equivalent benefit may occur by increasing the dose of one bronchodilator when side effects are not a limiting factor. Detailed assessments of this approach have not been carried out.

Increasing the dose of either a beta2-agonist or an anticholinergic, especially when given by a wet nebulizer, appears to provide subjective benefit in acute episodes (Evidence B). Some patients may request regular treatment with high-dose, nebulized bronchodilators, especially if they have experienced subjective benefit from this treatment during an exacerbation. Clear scientific evidence for this approach is lacking, but one option is to examine the

improvement in mean daily peak expiratory flow recording during 2 weeks of treatment in the home and continue with nebulizer therapy if a significant improvement occurs. In general, nebulized therapy for a stable patient is not appropriate unless it has been shown to be better than conventional dose therapy.

Glucocorticosteroids

Regular treatment with inhaled glucocorticosteroids does not modify the long-term decline in FEV_1 in patients with COPD. However, regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic COPD patients with an FEV_1 <50% predicted (Stage III Severe COPD and Stage IV Very Severe COPD) and repeated exacerbations (for example, 3 in the last three years) (Evidence A). This treatment has been shown to reduce the frequency of exacerbations and thus improve health status (Evidence A), and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients. Inhaled glucocorticosteroid combined with a long-acting $beta_2$-agonist is more effective than the individual components (Evidence A). Short-term treatment with a combined inhaled glucocorticosteroid and long-acting beta2-agonist resulted in greater control of lung function and symptoms than combined anticholinergic and short-acting beta2-agonist.

Many existing COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from long-term treatment with oral or inhaled glucocorticosteroids. There is mounting evidence, however, that a short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD.

Long-term treatment with oral glucocorticosteroids is not recommended in COPD (Evidence A). There is no evidence of long-term benefit from this treatment. Moreover, a side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in patients with advanced COPD.

Other Pharmacologic Treatments

Vaccines: Influenza vaccines can reduce serious illness and death in COPD patients by about 50%. Vaccines containing killed or live, inactivated viruses are recommended, and should be given once (in autumn) or twice (in autumn and winter) each year (Evidence A). A pneumococcal vaccine containing 23 virulent serotypes has been used but sufficient data to support its general use in COPD patients are lacking (Evidence B).

Alpha-1 Antitrypsin Augmentation Therapy: Young patients with severe hereditary alpha-1 antitrypsin deficiency and established emphysema may be candidates for alpha-1 antitrypsin augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for COPD that is unrelated to alpha-1 antitrypsin deficiency (Evidence C).

Antibiotics: The use of antibiotics, other than in treating infectious exacerbations of COPD and other bacterial infections, is not recommended (Evidence A).

Mucolytic (Mucokinetic, Mucoregulator) Agents: (ambroxol, erdosteine, carbocysteine, iodinated glycerol): Although a few patients with viscous sputum may benefit from mucolytics, the overall benefits seem to be very small. Therefore, the widespread use of these agents cannot be recommended on the basis of the present evidence (Evidence D).

Antioxidant Agents: Antioxidants, in particular N -acetylcysteine, have been shown to reduce the frequency of exacerbations and could have a role in the treatment of patients with recurrent exacerbations (Evidence B). However, before their routine use can be recommended, the results of ongoing trials will have to be carefully evaluated.

Immunoregulators (Immunostimulators, Immunomodulators): Studies using an immunostimulator in COPD show a decrease in the severity and frequency of exacerbations. However, additional studies to examine the long term effects of this therapy are required before regular use can be recommended (Evidence B).

Antitussives: Cough, although sometimes a troublesome symptom in COPD, has a significant protective role. Thus, the regular use of antitussives is contraindicated in stable COPD (Evidence D).

Vasodilators: In patients with stable COPD, inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance and thus is contraindicated.

Respiratory Stimulants: The use of doxapram, a non-specific respiratory stimulant available as an intravenous formulation, is not recommended in stable COPD (Evidence D). Almitrine bismesylate is not recommended for regular use in stable COPD patients (Evidence B).

Narcotics: The use of oral and parenteral opioids is effective for treating dyspnea in COPD patients with advanced disease. There are insufficient data to conclude whether nebulized opioids are effective. However, there are some clinical studies suggesting that morphine used to control dyspnea may have serious adverse effects and its benefits may be limited to a few sensitive subjects.

Others: Nedocromil, leukotriene modifiers, and alternative healing methods (e.g., herbal medicine, acupuncture, homeopathy) have not been adequately tested in COPD patients and thus cannot be recommended at this time.

Non-Pharmacologic Treatment

Rehabilitation

The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities. To accomplish these goals, pulmonary rehabilitation covers a range of non-pulmonary problems including exercise deconditioning, relative social isolation, altered mood states (especially depression), muscle wasting, and weight loss. COPD patients at all stages of disease benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue (Evidence A). The minimum length of an effective rehabilitation program is two months; the longer the program continues, the more effective the results. (Evidence B). However, as yet, no effective structure has been developed to maintain the effects over time. Benefits have been reported from rehabilitation programs conducted in inpatient, outpatient, and home settings.

Ideally, pulmonary rehabilitation should involve several types of health professionals. A comprehensive pulmonary rehabilitation program includes exercise training, nutrition counseling, and education. Baseline and outcome assessments of each participant in a pulmonary rehabilitation program should be made to quantify individual gains and target areas for improvement and should include:

- Detailed medical history and physical examination
- Measurement of spirometry before and after a bronchodilator drug
- Assessment of exercise capacity
- Measurement of health status and the impact of breathlessness
- Assessment of inspiratory and expiratory muscle strength and lower limb strength (e.g., quadriceps) in patients who suffer from muscle wasting (optional)

The first two assessments are important for establishing entry suitability and baseline status but are not used in outcome assessment. The last three assessments are baseline and outcome measures.

Oxygen Therapy

The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival (Evidence A). It can also have a beneficial impact on hemodynamics, hematologic characteristics, exercise capacity, lung mechanics, and mental state.

Long-term oxygen therapy is generally introduced in Stage IV Very Severe COPD for patients who have:

- PaO_2 at or below 7.3 kPa (55 mm Hg) or SaO_2 at or below 88%, with or without hypercapnia; or
- PaO_2 between 7.3 kPa (55 mm Hg) and 8.0 kPa (60 mm Hg) or SaO_2 89%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive heart failure, or polycythemia (hematocrit >55%).

The goal of long-term oxygen therapy is to increase the baseline PaO_2 to at least 8.0 kPa (60 mm Hg) at sea level and rest, and/or produce SaO_2 at least

90%, which will preserve vital organ function by ensuring an adequate delivery of oxygen.

A decision about the use of long-term oxygen should be based on the waking PaO_2 values. The prescription should always include the source of supplemental oxygen (gas or liquid), the method of delivery, duration of use, and the flow rate at rest, during exercise, and during sleep.

Ventilatory Support

To date there is no convincing evidence that mechanical ventilatory support has a role in the routine management of stable COPD.

Surgical Treatments

Bullectomy: In carefully selected patients, this procedure is effective in reducing dyspnea and improving lung function (Evidence C). A thoracic computed tomography scan, arterial blood gas measurement, and comprehensive respiratory function tests are essential before making a decision regarding a patient's suitability for resection of a bulla.

Lung Volume Reduction Surgery (LVRS): LVRS is a surgical procedure in which parts of the lung are resected to reduce hyperinflation. Results from large multicenter studies indicate that LVRS does not improve life expectancy but improves exercise capacity in patients with predominant upper lobe emphysema and a low post-rehabilitation exercise capacity, and may improve global health status in patients with heterogeneous emphysema. In some centers, with adequate experience, perioperative mortality of LVRS has been reported to be less than 5%. However, hospital costs associated with LVRS are high and it remains an experimental palliative surgical procedure not recommended for widespread use.

Lung Transplantation: In appropriately selected patients with very advanced COPD, lung transplantation has been shown to improve quality of life and functional capacity (Evidence C). Criteria for referral for lung transplantation include FEV_1 <35% predicted, PaO_2 <7.3-8.0 kPa (55-60 mm Hg), $PaCO_2$ >6.7 kPa (50mm Hg), and secondary pulmonary hypertension.

Special Considerations

Surgery in COPD: Postoperative pulmonary complications are as important and common as postoperative cardiac complications and, consequently, are a key component of increased risk of surgery in COPD patients. The principal potential factors contributing to the risk include smoking, poor general health status, age, obesity, and COPD severity. A comprehensive definition of postoperative pulmonary complications should include only major pulmonary respiratory complications, namely lung infections, atelectasis, and/or increased airflow obstruction, all potentially resulting in acute respiratory failure and aggravation of underlying COPD.

The surgical site is the most important predictor, and risk increases as the incision approaches the diaphragm. Upper abdominal and thoracic surgery represents the greatest risk, the latter being uncommon after interventions outside the thorax or abdomen. Most reports conclude that epidural or spinal anesthesia have a lower risk than with general anesthesia, although the results are not totally uniform. Patient-risk factors are identified by careful history, physical examination, chest radiography, and pulmonary function tests.

Several studies in high risk COPD patients suggest that there is threshold beyond which the risk of surgery is prohibitive. Surgery should be postponed if an exacerbation is present. Surgery in patients with COPD needs to be differentiated from that aimed to improve function and symptoms for COPD. This includes bullectomy, lung volume reduction surgery and lung transplantation.

V. Manage Exacerbations

Key Points

- Exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD.
- The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified (Evidence B).
- Inhaled bronchodilators (particularly inhaled beta2-agonists and/or anticholinergics), theophylline, and systemic, preferably oral, glucocorticosteroids are effective treatments for exacerbations of COPD (Evidence A).
- Patients experiencing COPD exacerbations with clinical signs of airway infection (e.g., increased volume and change of color of sputum, and/or fever) may benefit from antibiotic treatment (Evidence B).
- Noninvasive intermittent positive pressure ventilation (NIPPV) in exacerbations improves blood gases and pH, reduces in-hospital mortality, decreases the need for invasive mechanical ventilation and intubation, and decreases the length of hospital stay (Evidence A).

COPD is often associated with exacerbations of symptoms. The economic and social burden of COPD exacerbations is extremely high. The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified. The role of bacterial infections, once believed to be the main cause of COPD exacerbations, is controversial, but recent investigations with newer research techniques have begun to provide important information. Conditions that may mimic the symptoms of an exacerbation include pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and arrhythmia. Recommendations for use of antibiotics for COPD exacerbations are provided at the end of the "Major Recommendations" field.

Diagnosis and Assessment of Severity

Increased breathlessness, the main symptom of an exacerbation, is often accompanied by wheezing and chest tightness, increased cough and sputum, change of the color and/or tenacity of sputum, and fever. Exacerbations may also be accompanied by a number of nonspecific complaints, such as malaise, insomnia, sleepiness, fatigue, depression, and confusion. A decrease in exercise tolerance, fever, and/or new radiological anomalies suggestive of pulmonary disease may herald a COPD exacerbation. An increase in sputum volume and purulence points to a bacterial cause, as does a prior history of chronic sputum production.

The assessment of the severity of an exacerbation is based on the patient's medical history before the exacerbation, symptoms, physical examination, lung function tests, arterial blood gas measurements, and other laboratory tests. The medical history should cover how long worsening or new symptoms have been present, the frequency and severity of breathlessness and coughing attacks, sputum volume and color, limitation of daily activities, any previous episodes/exacerbations and whether they required hospitalization, and the present treatment regimen. When available, prior measurements of lung function and arterial blood gases are extremely useful for comparison with those made during the acute episode, as an acute change in these tests is more important than their absolute values. In patients with very severe COPD, the most important sign of severe exacerbation is a change in alertness of the patient and this signals a need for immediate evaluation in the hospital.

Lung Function Tests: Even simple lung function tests can be difficult for a sick patient to perform properly. In general, a PEF <100 liters per minute or an FEV_1 <1.00 liters indicates a severe exacerbation.

Assessment of Arterial Blood Gases: In the hospital, measurement of arterial blood gases is essential to assess the severity of exacerbation. A PaO_2 <8.0 kPa (60 mm Hg) and/or SaO_2 <90% with or without $PaCO_2$ greater than 6.7 kPa, 50 mm Hg (when breathing room air) indicates respiratory failure. In addition, PaO_2 <6.7 kPa (50 mm Hg), $PaCO_2$ >9.3 kPa (70 mm Hg), and pH <7.30 point towards a life-threatening episode that needs close monitoring or critical management.

Chest X-ray and Electrocardiogram (ECG): Chest radiographs (posterior/anterior plus lateral) are useful in identifying alternative diagnoses that can mimic the symptoms of an exacerbation. An electrocardiogram aids in the diagnosis of right ventricular hypertrophy, arrhythmias, or ischemic episodes. Pulmonary embolism can be very difficult to distinguish from an exacerbation, especially in severe COPD, because right ventricular hypertrophy and large pulmonary arteries lead to confusing electrocardiogram and radiographic results. Spiral computed tomography scanning and angiography and perhaps specific D-dimer assays are the best tools presently available for diagnosis of pulmonary embolism in patients with COPD but ventilation-perfusion scanning is of no value. A low systolic blood pressure and an inability to increase the PaO_2 above 8.0 kPa (60 mm Hg) despite high flow oxygen also suggest pulmonary embolism. If there are strong indications that pulmonary embolism has occurred, it is best to treat for this along with the exacerbation.

Other Laboratory Tests: The whole blood count may identify polycythemia (hematocrit >55%) or bleeding. White blood cell counts are usually not very informative. The presence of purulent sputum during an exacerbation of symptoms is sufficient indication for starting antibiotic treatment. Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis are the most common bacterial pathogens involved in COPD exacerbations. If an infectious exacerbation does not respond to initial antibiotic treatment, a sputum culture and an antibiogram should be performed. Biochemical tests can reveal whether the cause of the exacerbation is an electrolyte disturbance(s) (hyponatremia, hypokalemia, etc.), a diabetic crisis, or poor nutrition (low proteins), and may suggest a metabolic acid-base disorder.

Home Management

There is increasing interest in home care for end-stage COPD patients, although economic studies of home care services have yielded mixed results. A major outstanding issue is when to treat an exacerbation at home and when to hospitalize the patient.

Bronchodilator Therapy: Home management of COPD exacerbations involves increasing the dose and/or frequency of existing bronchodilator therapy (Evidence A). If not already used, an anticholinergic can be added until the symptoms improve. In more severe cases, high-dose nebulizer therapy can be given on an as-needed basis for several days and if a suitable nebulizer is available. However, long-term use of nebulizer therapy after an acute episode is not routinely recommended.

Glucocorticosteroids: Systemic glucocorticosteroids are beneficial in the management of exacerbations of COPD. They shorten recovery time and help to restore lung function more quickly (Evidence A), and may reduce the risk of early relapse. They should be considered in addition to bronchodilators if the patient's baseline FEV_1 is less than 50% predicted. A dose of 40 milligrams of prednisolone per day for 10 days is recommended (Evidence D). One large study indicates that nebulized budesonide may be an alternative to oral glucocorticosteroids in the treatment of nonacidotic exacerbations.

Hospital Management

The risk of dying from an exacerbation of COPD is closely related to the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support. Patients lacking these features are not at high risk of dying, but those with severe underlying COPD often require hospitalization in any case. Attempts at managing such patients entirely in the community have met with only limited success, but returning them to their homes with increased social support and a supervised medical care package after an initial emergency room assessment has been much more successful. However, detailed cost-benefit analyses of these approaches are awaited.

Indications for Hospital Assessment or Admission for Exacerbations of COPD*

- Marked increase in intensity of symptoms, such as sudden development of resting dyspnea
- Severe background COPD
- Onset of new physical signs (e.g., cyanosis, peripheral edema)
- Failure of exacerbation to respond to initial medical management
- Significant comorbidities
- Newly occurring arrhythmias
- Diagnostic uncertainty
- Older age
- Insufficient home support

*Local resources need to be considered.

Indications for Intensive Care Unit Admission of Patients with Exacerbations of COPD*

- Severe dyspnea that responds inadequately to initial emergency therapy.
- Confusion, lethargy, coma.
- Persistent or worsening hypoxemia (PaO_2 <5.3 kPa, 40 mm Hg), and/or severe/worsening hypercapnia ($PaCO_2$ >8.0 kPa, 60 mm Hg), and/or severe/worsening respiratory acidosis (pH <7.25) despite supplemental oxygen and noninvasive positive-pressure ventilation (NIPPV)

*Local resources need to be considered.

Some patients need immediate admission to an intensive care unit (ICU). Admission of patients with severe COPD exacerbations to intermediate or special respiratory care units may be appropriate if personnel, skills, and equipment are available to identify and manage acute respiratory failure successfully.

The first actions when a patient reaches the emergency department are to provide controlled oxygen therapy and to determine whether the exacerbation is life-threatening. If so, the patient should be admitted to the intensive care unit immediately. Otherwise, the patient may be managed in the emergency department or hospital as detailed below.

Management of Severe but Not Life-threatening Exacerbations of COPD in the Emergency Department or Hospital*

- Assess severity of symptoms, blood gases, chest x-ray.
- Administer controlled oxygen therapy and repeat arterial blood gas measurement after 30 minutes.
- Bronchodilators:
    - Increase doses or frequency.
    - Combine beta2-agonists and anticholinergics.
    - Use spacers or air-driven nebulizers.
    - Consider adding intravenous methylxanthine, if needed.
- Add glucocorticosteroids.
    - Oral or intravenous

- Consider antibiotics.
    - When signs of bacterial infection, oral or occasionally intravenous
- Consider noninvasive mechanical ventilation.
- At all times:
    - Monitor fluid balance and nutrition.
    - Consider subcutaneous heparin.
    - Identify and treat associated conditions (e.g., heart failure, arrhythmias).
    - Closely monitor condition of the patient.

*Local resources need to be considered.

Controlled Oxygen Therapy: Oxygen therapy is the cornerstone of hospital treatment of COPD exacerbations. Adequate levels of oxygenation (PaO_2 >8.0 kPa, 60 mm Hg or SaO_2 >90%) are easy to achieve in uncomplicated exacerbations, but CO_2 retention can occur insidiously with little change in symptoms. Once oxygen is started, arterial blood gases should be checked 30 minutes later to ensure satisfactory oxygenation without CO_2 retention or acidosis. Venturi masks are more accurate sources of controlled oxygen than are nasal prongs but are more likely to be removed by the patient.

Bronchodilator Therapy: Short-acting, inhaled beta2-agonists are usually the preferred bronchodilators for the treatment of exacerbations of COPD (Evidence A). If a prompt response to these drugs does not occur, the addition of an anticholinergic is recommended, even though evidence concerning the effectiveness of this combination is controversial. Despite its widespread clinical use, the role of aminophylline in the treatment of COPD exacerbations remains controversial. Most studies of aminophylline have demonstrated minor improvements in lung volumes without showing gas exchange deterioration. In more severe exacerbations, addition of an oral or intravenous methylxanthine to the treatment can be considered. However, close monitoring of serum theophylline is recommended to avoid the side effects of these drugs. Possible beneficial effects in lung function, and clinical endpoints, are modest and inconsistent, whereas adverse effects are significantly increased.

Glucocorticosteroids: Oral or intravenous glucocorticosteroids are recommended as an addition to bronchodilator therapy, (plus eventually antibiotics and oxygen therapy) in the hospital management of exacerbations of COPD (Evidence A). The exact dose that should be given is not known, but high doses are associated with a significant risk of side effects. Thirty to 40 milligrams of oral prednisolone daily for 10 to 14 days is a reasonable compromise between efficacy and safety (Evidence D). Prolonged treatment does not result in a greater efficacy and increases the risk of side effects.

Ventilatory Support: The primary objectives of mechanical support in patients with exacerbations in Stage IV Very Severe COPD are to decrease mortality and morbidity and to relieve symptoms. Ventilatory support includes both noninvasive mechanical ventilation using either negative or positive pressure devices and invasive (conventional) mechanical ventilation by oro-/nasotracheal tube or tracheostomy.

Noninvasive Mechanical Ventilation: Noninvasive positive pressure ventilation (NIPPV) has been studied in many uncontrolled and five randomized controlled trials in acute respiratory failure. The studies show consistently positive results with success rates of 80-85%. Taken together they provide evidence that noninvasive positive pressure ventilation increases pH, reduces $PaCO_2$, reduces the severity of breathlessness in the first 4 hours of treatment, and decreases the length of hospital stay (Evidence A). More importantly, mortality -- or its surrogate, intubation rate -- is reduced by this intervention. However, noninvasive positive pressure ventilation is not appropriate for all patients, as summarized below.

Indications and Relative Contraindications for NIPPV

Selection criteria

- Moderate to severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Moderate to severe acidosis (pH <7.35) and hypercapnia ($PaCO_2$ >6.0 kPa, 45 mm Hg)
- Respiratory frequency >25 breaths per minute

Exclusion criteria

- Respiratory arrest
- Cardiovascular instability (hypotension, arrhythmias, myocardial infarction)
- Somnolence, impaired mental status, uncooperative patient
- High aspiration risk; viscous or copious secretions
- Recent facial or gastroesophageal surgery
- Craniofacial trauma, fixed nasopharyngeal abnormalities
- Extreme obesity

Invasive (Conventional) Mechanical Ventilation: Patients who show impending acute respiratory failure and those with life-threatening acid-base status abnormalities and/or altered mental status despite aggressive pharmacologic therapy are likely to be the best candidates for invasive mechanical ventilation. The indications for initiating mechanical ventilation during exacerbations of COPD are shown below, the first being the commonest and most important reason. The three ventilatory modes most widely used are assisted-control ventilation, and pressure support ventilation alone or in combination with intermittent mandatory ventilation.

Indications for Invasive Mechanical Ventilation:

- Severe dyspnea with use of accessory muscles and paradoxical abdominal motion
- Respiratory frequency >35 breaths per minute
- Life-threatening hypoxemia (PaO_2 <5.3 kPa, 40 mm Hg or PaO_2/FiO_2 <200 mm Hg)
- Severe acidosis (pH <7.25) and hypercapnia ($PaCO_2$ >8.0 kPa, 60 mm Hg)
- Respiratory arrest

- Somnolence, impaired mental status
- Cardiovascular complications (hypotension, shock, heart failure)
- Other complications (metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion)
- Noninvasive positive pressure ventilation failure (or exclusion criteria, above)

The use of invasive ventilation in end-stage COPD patients is influenced by the likely reversibility of the precipitating event, the patient's wishes, and the availability of intensive care facilities. Major hazards include the risk of ventilator-acquired pneumonia (especially when multi-resistant organisms are prevalent), barotrauma, and failure to wean to spontaneous ventilation. Contrary to some opinions, mortality among COPD patients with respiratory failure is no greater than mortality among patients ventilated for non-COPD causes. When possible, a clear statement of the patient's own treatment wishes -- an advance directive or "living will" -- makes these difficult decisions much easier to resolve.

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD, and the best method to wean patients from the ventilator remains a matter of debate. Whether pressure support or a T-piece trail is used, weaning is shortened when a clinical protocol is adopted (Evidence A). Noninvasive ventilation has been applied to facilitate the weaning process in COPD patients with acute or chronic respiratory failure. Compared with invasive pressure support ventilation, noninvasive positive pressure ventilation (NIPPV) during weaning shortened weaning time, reduced the stay in the intensive care unit, decreased the incidence of nosocomial pneumonia, and improved 60-day survival rates. Similar findings have been reported when noninvasive positive pressure ventilation is used after extubation for hypercapnic respiratory failure (Evidence C).

Other Measures: Further treatment measures that can be used in the hospital include: fluid administration (accurate monitoring of fluid balance is essential); nutrition (supplementary when the patient is too dyspneic to eat); low molecular weight heparin in immobilized, polycythemic, or dehydrated patients with or without a history of thromboembolic disease; sputum clearance (by stimulating coughing and low volume forced expirations as in home management). Manual or mechanical chest percussion and postural drainage may be beneficial in patients producing >25 mL sputum per day or with lobar atelectasis.

Hospital Discharge and Follow-up

Insufficient clinical data exist to establish the optimal duration of hospitalization for exacerbations of COPD. Consensus and limited data support the discharge criteria listed below:

Discharge Criteria for Patients with Exacerbations of COPD

- Inhaled beta2-agonst therapy is required no more frequently than every 4 hours

- Patient, if previously ambulatory, is able to walk across room.
- Patient is able to eat and sleep without frequent awakening by dyspnea.
- Patient has been clinically stable for 12 to 24 hours.
- Arterial blood gases have been stable for 12 to 24 hours.
- Patient (or home caregiver) fully understands correct use of medications.
- Follow-up and home care arrangements have been completed (e.g., visiting nurse, oxygen delivery, meal provisions).
- Patient, family, and physician are confident patient can manage successfully

Follow-up Assessment 4 to 6 weeks After Discharge from Hospital for Exacerbations of COPD

- Ability to cope in usual environment
- Measurement of FEV_1
- Reassessment of inhaler technique
- Understanding of recommended treatment regimen
- Need for long-term oxygen therapy and/or home nebulizer (for patients with severe COPD

Thereafter, follow-up is the same as for stable COPD, including supervising smoking cessation, monitoring the effectiveness of each drug treatment, and monitoring changes in spirometric parameters. Home visits by a community nurse may permit earlier discharge of patients hospitalized with a non-acidotic exacerbation of COPD, without increasing readmission rate. Early outpatient pulmonary rehabilitation after hospitalization for COPD exacerbation results in exercise capacity and health status improvements at three months.

If hypoxemia developed during the exacerbation, arterial blood gases should be rechecked at discharge and at the follow-up visit. If the patient remains hypoxemic, long-term oxygen therapy should be instituted. Decisions about continuous domiciliary oxygen based on the severity of the acute hypoxemia during an exacerbation are frequently misleading.

The opportunities for prevention of future exacerbations should be reviewed before discharge with particular attention to future influenza vaccination plans, knowledge of current therapy including inhaler technique, and how to recognize symptoms of exacerbations. Pharmacotherapy known to reduce the number of exacerbations should be considered. Social problems should be discussed and principal caregivers identified if the patient has a significant persisting disability.

Antibiotics

Randomised placebo controlled studies of antibiotic treatment in exacerbations of COPD have demonstrated a small beneficial effect of antibiotics on lung function, and one randomised controlled trial has provided evidence for a significant beneficial effect of antibiotics in COPD patients who presented with an increase in all three of the following cardinal symptoms:

dyspnea, sputum volume, sputum purulence. There was also some benefit in those patients with an increase in only two of these cardinal symptoms.

A study on non-hospitalized patients with exacerbations of COPD showed a relationship between the purulence of the sputum and the presence of bacteria, suggesting that these patients should be treated with antibiotics if they also have at least one of the other two cardinal symptoms (dyspnea or sputum volume). However, these criteria for exacerbations of COPD have not been validated in other studies. A study in COPD patients with exacerbations requiring mechanical ventilation (invasive and non-invasive) indicated that not giving antibiotics was associated with increased mortality and a greater incidence of secondary intra-hospital pneumonia.

Based on the current available evidence, antibiotics should be given to:

- Patients with exacerbations of COPD with three of the following cardinal symptoms: increased dyspnea, increased sputum volume, increased sputum purulence (Evidence B)
- Patients with exacerbations of COPD with two of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms (Evidence C)
- Patients with a severe exacerbation of COPD that requires invasive mechanical ventilation (invasive and non-invasive) (Evidence B)

The predominant bacterial organisms recovered in the lower airways of patients with mild exacerbations are Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis. In contrast, studies in patients requiring mechanical ventilation with severe underlying COPD have shown that other microorganisms, such as enteric gram negative bacilli and Pseudomonas aeruginosa may be more frequent. Other studies have shown that the severity of the COPD is an important determinant of the type of microorganism. In patients with mild COPD, S. pneumoniae is predominant. When the FEV_1 is lower, H. influenzae and M. catarrhalis are more frequent and P. aeruginosa may appear in patients with a more severe degree of airways obstruction (see table below). The risk factors for P. aeruginosa infection are recent hospitalisation, frequent administration of antibiotics (4 courses in the last year), very severe COPD (Stage IV), and isolation of P. aeruginosa during a previous exacerbation or colonization during a stable period.

Stratification of Patients with COPD Exacerbated for Antibiotic Treatment and Potential Microorganisms Involved in Each Group		
Group[a]	Definition[b]	Microorganisms
Group A: Patients not requiring hospitalization (Stage I: Mild COPD)	Mild exacerbation	H. influenzae S. pneumonia M. catarrhalis Chlamydia pneumoniae[c] Viruses
Group B: Patients admitted to hospital (Stages II-IV: Moderate	Moderate-severe exacerbation without risk factors for P.	Group A plus: Enterobacteriaceae (K. pneumoniae, E. coli,

Stratification of Patients with COPD Exacerbated for Antibiotic Treatment and Potential Microorganisms Involved in Each Group		
Group[a]	Definition[b]	Microorganisms
to Very Severe COPD)	aeruginosa infection	Enterobacter, etc.)
Group C: Patients admitted to hospital (Stages II-IV: Moderate to Very Severe COPD)	Moderate-severe exacerbation with risk factors for P. aeruginosa infection	Group B plus: P. aeruginosa

[a] In some settings, patients with moderate to severe exacerbations may be treated as outpatients. In this case, patients may best be stratified into two groups: an uncomplicated group without any risk factors and a complicated group that has one or more "risk factors" (comorbidity, severe COPD, frequent exacerbations, antimicrobial use within last 3 months). The uncomplicated group: use Group A recommendations in the table below. Complicated group: use Group B or C recommendations (oral treatment) in the table below.

[b] Severity refers to the exacerbation, though this is intertwined with the severity of the underlying COPD.

[c] Chlamydia pneumonia (or Chlamidophila pneumoniae) has not been confirmed as a cause of exacerbation in some areas (e.g., UK).

There is no clear information about when to use oral or intravenous (IV) route of administration in hospitalized patients. The route of administration depends on the ability of the patient to eat and the pharmacokinetics of the antibiotic. The oral route is preferred. Otherwise, the IV route has to be used, switching to oral when there is clinical stabilization. Antibiotic treatment in patients with exacerbations of COPD should be maintained for 3 to 10 days. The table below provides recommended antibiotic treatment in exacerbations of COPD.

Ten to thirty percent of COPD exacerbated patients do not respond to empiric antimicrobial treatment. In such cases the patient should be re-evaluated for complications that can aggravate symptoms and mimic exacerbations (e.g., cardiac failure, pulmonary embolism, non-compliance with prescribed medications); microbiological reassessment of these patients is recommended.

Antibiotic Treatment in Exacerbations of COPD[a,b]			
	Oral Treatment (No particular order)	Alternative (No particular order)	Parenteral Treatmer (No particular order)
Group A	Patients with only one cardinal symptom should not receive antibiotics. If indication, then: • Beta-lactam (Ampicillin/Amoxicillin[c]) • Tetracycline • Trimethoprim/ Sulfamethoxazole	• Beta-lactam/ Beta-lactamase inhibitor (Co-amoxiclav) • Macrolides (Azithromycin, Clarithromycin, Roxithromycin[d]) • Cephalosporins -- 2nd or 3rd generation • Ketolides (Telithromycin)	

Antibiotic Treatment in Exacerbations of COPD[a,b]			
	Oral Treatment (No particular order)	Alternative (No particular order)	Parenteral Treatmer (No particular order)
Group B	• Beta-lactam/beta-lactamase inhibitor (Co-amoxiclav)	• Fluoroquinolones[d] (Gatifloxacin, Gemifloxacin, Levofloxacin, Moxifloxacin)	• Beta-lac beta-lactamase (Co-amoxiclav, ampicillin/ sulb • Cephalo 2nd or 3rd gener • Fluoroqu (Gatifloxacin, Levofloxacin, Moxifloxacin)
Group C	• Fluoroquinolones (Ciprofloxacin, Levofloxacin – high dose[e])		• Fluoroqu (Ciprofloxacin, Levofloxacin -- dose[e]) or • Beta-lac P. aeruginosa a

[a] All patients with symptoms of a COPD exacerbation should be treated with additional bronchodilators ± glucocorticosteroids.

[b] Classes of antibiotics are provided (with specific agents in parentheses). In countries with high incidence of S. pneumoniae resistant to penicillin, high dosages of Amoxicillin or Co-Amoxiclav are recommended. (See table above for definitions of Groups A, B, C.)

[c] This antibiotic is not appropriate in areas where there is increased prevalence of beta-lactamase producing H. influenzae and M. catarrhalis, and/or of S. pneumoniae resistance to penicillin.

[d] Not available in all areas of the world

[e] Dose 750 mg effective against P. aeruginosa

Definitions:

Description of Levels of Evidence

A. Randomized controlled trials (RCTs). Rich body of data.
   Definition: Evidence is from endpoints of well-designed RCTs that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B. RCTs. Limited data.
   Definition: Evidence is from endpoints of intervention studies that include only a limited number of patients, posthoc or subgroup analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.

C. Nonrandomized trials. Observational studies.
Definition: Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.

D. Panel consensus. Judgment.
Definition: This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was deemed insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above-listed criteria.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is specifically stated for selected recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Chronic obstructive pulmonary disease (COPD) prevention
- The goals of effective COPD management are to:
    - Prevent disease progression
    - Relieve symptoms
    - Improve exercise tolerance
    - Improve health status
    - Prevent and treat complications
    - Prevent and treat exacerbations
    - Reduce mortality

POTENTIAL HARMS

Beta2-agonists: Stimulation of beta2-receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in very susceptible patients, although this appears to be a remarkably rare event with inhaled therapy. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta2-agonists, whatever the route of administration, and this limits the dose that can be tolerated.

Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics, and oxygen consumption can be increased under resting conditions, these metabolic effects show tachyphylaxis unlike the bronchodilator actions. Mild falls in PaO_2 occur after administration of both short- and long-acting beta2-agonists, but the clinical significance of these changes is doubtful. Despite the concerns raised some years ago, further detailed study has found no

association between beta2-agonist use and an accelerated loss of lung function or increased mortality in COPD.

Anticholinergics: Anticholinergic drugs, such as ipratropium, oxitropium and tiotropium bromide, are poorly absorbed, which limits the troublesome systemic effects seen with atropine. Extensive use of this class of inhaled agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of the mouth. Twenty-one days of inhaled tiotropium, 18 micrograms a day as a dry powder, does not retard mucus clearance from the lungs. Although occasional prostatic symptoms have been reported, there are no data to prove a true causal relationship. A bitter, metallic taste is reported by some patients using ipratropium. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported and requires further investigation.

Use of wet nebulizer solutions with a face mask has been reported to precipitate acute glaucoma, probably by a direct effect of the solution on the eye. Mucociliary clearance is unaffected by theses drugs, and respiratory infection rates are not increased.

Methylxanthines: Toxicity is dose related, a particular problem with the xanthine derivatives because their therapeutic ratio is small and most of the benefit occurs only when near-toxic doses are given. Methylxanthines are nonspecific inhibitors of all phosphodiesterase enzyme subsets, which explains their wide range of toxic effects. Problems include the development of atrial and ventricular arrhythmias (which can prove fatal) and grand mal convulsions (which can occur irrespective of prior epileptic history). More common and less dramatic side effects include headaches, insomnia, nausea, and heartburn, and these may occur within the therapeutic range of serum theophylline. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose (either intentional or accidental).

Oral Glucocorticosteroids: A side effect of long-term treatment with systemic glucocorticosteroids is steroid myopathy, which contributes to muscle weakness, decreased functionality, and respiratory failure in subjects with advanced COPD.

CONTRAINDICATIONS

CONTRAINDICATIONS

Special consideration should be given before using pharmacotherapy in selected populations: people with medical contraindications, light smokers fewer than 10 cigarettes/day, and pregnant and adolescent smokers.

Vasodilators: In patients with stable chronic obstructive pulmonary disease, inhaled nitric oxide can worsen gas exchange because of altered hypoxic regulation of ventilation-perfusion balance and thus is contraindicated.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Foreign Language Translations
Patient Resources
Pocket Guide/Reference Cards
Slide Presentation
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization, National Heart, Lung and Blood Institute; 2005. 115 p. [62 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 (revised 2005)

GUIDELINE DEVELOPER(S)

Global Initiative for Chronic Obstructive Lung Disease (GOLD)
National Heart, Lung, and Blood Institute (U.S.) - Federal Government Agency [U.S.]
World Health Organization - International Agency

GUIDELINE DEVELOPER COMMENT

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) is a collaborative project of the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO).

SOURCE(S) OF FUNDING

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GUIDELINE COMMITTEE

Global Initiative for Chronic Obstructive Lung Disease (GOLD) Executive Committee
Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Panel

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Global Initiative for Chronic Obstructive Lung Disease (GOLD) Executive Committee (2001): A. Sonia Buist MD; Peter Calverley, MD; Bartolome R. Celli, MD; Leonardo Fabbri, MD; Yoshinosuke Fukuchi, MD; Larry Grouse; Suzanne Hurd (Scientific Director of GOLD); Christine Jenkins, MD; Nikolai Khaltaev, MD; Claude Lenfant, MD (Director, National Heart, Lung, and Blood Institute, National Institutes of Health, USA); Juan Luna, MD; William MacNee, MD; Romain Pauwels, MD, Ph.D.; Nan-Shan Zhong, MD

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

ENDORSER(S)

American Thoracic Society - Medical Specialty Society

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Global Initiative for Chronic Obstructive Lung Disease (GOLD), World Health Organization (WHO), National Heart, Lung and Blood Institute (NHLBI). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization, National Heart, Lung and Blood Institute; 2004. 100 p.

Each year, a new updated report will be posted; a revision of the entire document will be prepared approximately every 5 years. According to the developer, a revision of the entire document has been initiated and is scheduled to be completed in 2006.

Information regarding GOLD, Phase IV is available at the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Web site.

GUIDELINE AVAILABILITY

Electronic copies: Available from the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Web site.

Print copies: Available from the National Heart, Lung, and Blood Institute, Information Center, P.O. Box 30105, Bethesda, MD 20824-0105 and the Global Initiative for Obstructive Pulmonary Disease Secretariat, Romain Pauwels, M.D., Ph.D., University Hospital, Department of Respiratory Diseases, De Pintelaan 185, B 9000 Ghent BELGIUM; Fax: (32) 9/240 23 41.

AVAILABILITY OF COMPANION DOCUMENTS

The following summary is available:

- Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Executive summary. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization/National Heart, Lung, and Blood Institute; 2005. 45 p. Electronic copies: Available from the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Web site.

The following are also available:

- Pocket guide to COPD diagnosis, management, and prevention. Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute, 2005. Electronic copies: Available from the GOLD Web site.
- GOLD teaching slide Set. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization/National Heart, Lung, and Blood Institute; 2005. Various pagings. Electronic copies: Available from the GOLD Web site.

- GOLD at-a-glance outpatient COPD management reference. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization/National Heart, Lung, and Blood Institute; 2005. 8 p. Electronic copies: Available from the GOLD Web site.
- Spirometry for diagnosis of COPD. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization/National Heart, Lung, and Blood Institute; 2003. 4 p. Electronic copies: Available from the GOLD Web site.
- GOLD knowledge quiz. Bethesda (MD): Global Initiative for Chronic Obstructive Lung Disease, World Health Organization/National Heart, Lung, and Blood Institute; various pagings. Electronic copies: Available from the GOLD Web site.

Print copies: Available from the National Heart, Lung, and Blood Institute, Information Center, P.O. Box 30105, Bethesda, MD 20824-0105 and the Global Initiative for Obstructive Pulmonary Disease Secretariat, Romain Pauwels, M.D., Ph.D., University Hospital, Department of Respiratory Diseases, De Pintelaan 185, B 9000 Ghent BELGIUM Fax: (32) 9/240 23 41.

PATIENT RESOURCES

The following is available:

- GOLD inhaler charts and instructions. Global Initiative for Chronic Obstructive Lung Disease, World Health Organization/National Heart, Lung, and Blood Institute; 2001. (Many of the illustrations are adopted from those distributed by the National Asthma and Respiratory Training Center [NARTC], UK). Electronic copies: Available from the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Web site.
- GOLD patient guide: what you can do about a lung disease called COPD. Global Initiative for Chronic Obstructive Lung Disease, World Health Organization/National Heart, Lung, and Blood Institute; 2003. Electronic copies: Available in Portable Document Format (PDF) from the GOLD Web site. Also available in Italian from the GOLD Web site.

NGC STATUS

This summary was completed by ECRI on May 22, 2001. This summary was updated by ECRI on August 18, 2004, and on October 5, 2005. This summary was updated by ECRI on December 5, 2005 following the U.S. Food and Drug Administration (FDA) advisory on long-acting beta2-adrenergic agonists (LABA). This summary was updated by ECRI on January 27, 2006 following the U.S. Food and Drug Administration (FDA) advisory on Ketek (telithromycin). This summary was updated by ECRI on February 21, 2006 following the U.S. Food and Drug

Administration (FDA) advisory on Tequin (gatifloxacin). This summary was updated by ECRI on July 3, 2006 following the updated U.S. Food and Drug Administration (FDA) advisory on Ketek (telithromycin).

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